A CRITICAL SUMMARY OF RECENT LITERATURE ON PLASMA-CELLS AND MAST-CELLS.

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The two classes of cells which are the subject of this paper have been studied with much care during the past few years and by numerous observers. It is hoped that a summary of the facts they have recorded will be considered timely. The significance and functions of these cells are still problematical for the most part. However, we may be quite certain that they have important work to do, and we may confidently expect to have much light upon them in the near future.

Plasma-cells.

In 1891 Unna[32] described the elements which he called "plasma-cells," believing them to be the same as certain granular connective tissue cells, to which Waldeyer had previously given this name. Later studies indicated that the two were not identical, and Waldeyer[40] advised the restriction of the term "plasma-cell" to that of Unna, finding that the structures named by himself (Waldeyer) corresponded, at least in large part, with the "mast-cells" of Ehrlich, which will be considered below.

Morphology. The plasma-cells of Unna are peculiar in having *protoplasm* that is stained by basic aniline dyes. With Unna's polychrome methylene-blue (described hereafter) the plasma-cells are stained blue-violet, while their nuclei are blue, according to most writers. The outer part of the protoplasm stains more deeply than the inner part, leaving a pale zone around the nucleus. Unna first described the plasma-cell as containing numerous stained granules in its protoplasm. Such granules have not been seen by most other observers. It is not uncommon, however, to find plasma-cells whose protoplasm is not homogeneous, but which contain small clumps and particles that stain somewhat unequally and irregularly.[19] The nucleus is round or oval, and is usually placed eccentrically. Five to eight deeply stained masses of chromatin are arranged chiefly about the border of the nucleus. Some observers have described a nucleolus. The appearance of the nucleus depends much on the manner of staining and decolorizing. Two or more nuclei are occasionally present. In size the plasma-cells vary from being of the dimensions of leucocytes to much larger—average diameter 6–7 μ × 8–10 μ.[17] In shape they are round, oval, roughly cubical or elongated, according to whether or not they are limited by connective tissue fibres or the pressure of other cells. Krompecher's[19] illustrations of the different forms of plasma-cells are excellent. The above description of the plasma-cell differs somewhat from Unna's and follows that of v. Marschalkó[23] and others who have written on this subject more recently. Undoubted indirect cell-division seems to have been observed only by Councilman[9] and Mallory,[22] but amitotic division has often been mentioned.[19] Degenerative changes in plasma-cells have been described by a number of observers.[33 19 9]

Cells whose protoplasm may be stained, but which differ from plasma-cells more or less in other respects—"pseudoplasma-cells"—have been described.[13 19] Their significance is at present not clear.

OCCURRENCE. Although they were supposed at first to belong only to pathological conditions, plasma-cells have been reported as occurring in lymph-nodes, in the lymphoid tissues of the spleen, and in the bone-marrow, both in man and the lower animals,[16] in ligaments,[28] in the framework of mucous glands of the tongue,[17] and especially in large numbers in the mucosa of the stomach and intestine in man.[9] Information as to their frequency and distribution in normal tissues is not very full. On the other hand, much has been written concerning their occurrence in diseased conditions, and a mere enumeration of these conditions would require several pages. A description of the pathological histology of any lesion can hardly be considered complete now which does not take account of the plasma-cells, if they are present.

Unna's first accounts of plasma-cells were based on sections of lupus. He early directed attention to tumor-like collections of these cells; such a collection he called a "plasmoma." It has appeared since that plasma-cells are abundant in the lesions of tuberculosis, wherever situated, in those of syphilis, leprosy, actinomycosis, and rhinoscleroma[39]—*i. e.*, the so-called "infectious granulomata." They are also frequently seen in large numbers in the stroma of carcinoma. In the main they are most characteristic of rather chronic processes, where they constitute an important part of what is usually termed round-cell infiltration. In acute inflammatory conditions, and especially in acute suppuration, they appear in smaller numbers, or are absent.[17] But v. Marschalkó[23] and Joannovics[17] were able to demonstrate plasma-cells in acute inflammatory lesions artificially produced in animals. Justi[18] found them in recent granulating wounds in man and the dog. Mallory[22] found them in the lesions of typhoid fever in the intestines, spleen, lymph-nodes, etc. According to Councilman,[9] plasma-cells constitute the bulk of the cell-infiltration in acute interstitial nephritis.

The study of the plasma-cells in the diseases of the skin has been carried on by Unna with great energy, and for the results of his work his *Histopathology of the Skin*[39] may be consulted.

ORIGIN, SIGNIFICANCE, AND FUNCTION. Concerning the origin of the plasma-cells, Unna[32] maintained that they were derived from connective tissue cells, stating that he was able to detect all the necessary transitional forms between the two. Most observers, however, believe that the plasma-cells are derived from the lymphocytes, chiefly the small mononuclear variety.[9 16 17 18 19 23 28] Possibly a few originate from polynuclear leucocytes.[19 17] Furthermore, it is claimed that the plasma-cells may become changed to connective tissue cells, and thus aid in the formation of fibrous tissue.[23 19 28 12] This latter hypothesis would make the production of connective-tissue cells from lymphocytes possible under certain circumstances, the plasma-cells being an intermediate form. It would modify existing ideas very considerably, and convincing proofs will be demanded before it can be accepted. It rests in part upon the same evidence as the theory of Unna above mentioned, namely, the existence of what appear to be transitional forms between plasma-cells and connective tissue cells. For a full discussion of this question, see the papers of Krompecher[19] and v. Marschalkó.[23]

Joannovics[17] takes a middle ground, believing that part of the plasma-cells come from lymphocytes and part from connective-tissue cells; the latter may become connective tissue cells again, while the former undergo degenerations of various sorts. It is not claimed by anyone, I believe, that all or most plasma-cells are destined to become connective tissue cells. The function or significance of these bodies is, therefore, at present uncertain. It is to be noted that they are not distinctive of any particular disease or class of diseases. Their absence from acute suppuration is remarkable. According to Councilman[9] and Mallory[22] they have amœboid properties; they may occur inside the bloodvessels, and may emigrate from the vessels by amœboid movement. Howard[15] states that he has demonstrated that plasma-cells may become transformed into typical eosinophiles, basing his opinion chiefly upon his studies of a case of trichinosis.

If the derivation of plasma-cells from lymphocytes be accepted, we shall have another clue to the origin of the cells in inflammatory exudates. Unna regarded the plasma-cells as being the expression of a degenerative change, whereas v. Marschalkó[23] considered them as evidence of progressive activity in the protection of the organism. Justi[18] thought it likely that they serve to eliminate some unknown substance by way of the lymphatics. Joannovics[17] suggested that their staining properties may be due to their having taken up chromatin from other and degenerated cells.

MAST-CELLS.

The term "mast-cells" was applied by Ehrlich[10] to large cells occurring in connective tissues, the protoplasm of which contained good-sized granules with marked affinity for basic aniline dyes (basophile granules, γ granules of Ehrlich). The name was considered appropriate because these cells occurred abundantly in conditions of congestion and chronic inflammation, and under other circumstances where he supposed nutrition to be heightened. It has already been stated that the plasma-cell of Waldeyer corresponds in the main with the mast-cell of Ehrlich. In size the mast-cells vary from that of a large leucocyte to many times those dimensions. They may be rounded, or they may present extremely irregular figures, which are determined apparently by the cavities of the tissue which they occupy. Forms shaped like an hour-glass or with several long, sinuous processes are common; they remind the observer of the outlines of a moving amœba. Their occasional occurrence in the epithelial layers of the skin can hardly be explained except by supposing that they have the power of amœboid movement.[2, 3] There is a relatively small, round nucleus, somewhere near the middle of the cell, which is usually in part, and sometimes wholly, obscured by the granules. Karyokinesis seems not to have been observed.[2, 3] The granules are the most striking characteristic, as they are usually good-sized, stain rapidly and intensely with the basic aniline dyes, and are decolorized with difficulty. They may be stained by Gram's method, and when they are large, as they are usually quite uniform in size, they may easily be mistaken for micrococci. The granules will sometimes retain the dye when the ordinary methods for staining the tubercle bacillus are used. Furthermore, the granules exhibit with stains the phenomenon of metachromism—*i. e.*, of presenting a shade of color more or less different from that which the dye imparts to the nuclei of the mast-cells and of the other elements of the tissue. The metachromism is most marked with thionin and toluidin-blue. These dyes stain the nuclei of cells of all sorts of blue, while the granules of the mast-cells are violet to red. The metachromism is reported to be very marked with kresyl-violet R.[11] The granules of the mast-cells are said by some to have a certain amount of affinity for acid dyes.[4, 5] Granular mast-cells are sometimes seen which are surrounded by a stained halo of the same color as the granules;[11, 14, 39] also free granules in the vicinity of mast-cells, and mast cells with protoplasm that stains as well as the granules.

The nature of these granules is undetermined. Hoyer[14] tentatively revived an earlier theory of Raudnitz, to the effect that the granules consisted of mucin. After an exhaustive study of the staining properties of mucin, he found that the metachromism shown by mucin and by the granules of mast-cells after thionin staining was very similar.

Unna[36 33] appears to regard this view with favor; it has recently been advocated by Harris[12]. It is to be noted that mucin is extremely capricious in exhibiting metachromism, and that the products of amyloid and other degenerations also show varying degrees of metachromism.

Basophilic granules may occur in blood-cells which are not mast-cells, as in the lymphocytes of normal blood after prolonged staining,[23] and the perinuclear basophilic granules described by Neusser.[6] According to Litten,[20] basophilic granules occur sometimes in the red blood-corpuscles in cases of anæmia; they differ from the granules of the mast-cells in not being metachromatic.

OCCURRENCE. Unlike plasma-cells, the mast-cells are very widely distributed in normal tissues. They have been observed in many different vertebrates, from the frog to man. According to Ehrlich,[10] the mast-cells are likely to be found just under epithelial surfaces, and immediately about the bloodvessels. They appear in the blood of the frog, and are abundant in the frog's tongue. In those animals in which mast-cells occur at all they are likely to be especially numerous in the tongue, as in the case of the bat; in the striped muscles generally they are not numerous, nor are they particularly so in the heart.[10] The rabbit, hare, and guinea-pig are remarkable for the small number of mast-cells in their tissues.[10]

In man the mast cells occur at all periods of life,[26] even in the new-born.[2] While they are comparatively uncommon in early infancy, they are always more or less numerous in the adult. In normal blood they are present in very small numbers and are probably derived from bone-marrow.[11] They constitute part of the cells of bone-marrow. They occur between the fibres of uterine muscle[27] and of the muscle of the intestine. They are usually to be found in the mucous membranes, where they are often numerous. They always occur in the skin, frequently in abundance. They are seen in the tissues of the normal resting mammary gland,[8] also in the active mamma, and, according to Unger,[30] are important in the transportation of fat in the mamma. They occur in the testicle, except in infants under about four months of age.[24] In pathological conditions they exhibit a certain amount of parallelism with plasma-cells in the manner of their occurrence. They are not characteristic of acute inflammation, especially not of acute suppuration.[26] However, Neisser[11] saw a case of gonorrhœa in which the pus consisted only of mast-cells. Also, according to Coen,[7] they appear in the skin in increased numbers, as the result of the application of strong solutions of iodine. They are often numerous about the lesions of chronic infectious processes, such as tuberculosis, but not necessarily; and they are by no means as characteristic of them as are plasma-cells. They are frequently abundant in the stroma of carcinoma, especially of the breast and skin where the fibrous tissue is plentiful. They are generally numerous in uterine fibromyomata[27] and in neurofibromata,[39] and in processes where cicatricial fibrous tissue is forming, as cicatrizing gastric ulcer. They are usually abundant in the mucous membranes of chronic catarrhs, and in the lung of cyanotic induration.[10] According to Ehrlich,[10] stagnation of the lymph-stream favors their accumulation, as in elephantiasis. Cells with basophilic granules occur in normal blood in very small numbers, and are usually supposed to be the same as mast-cells; in leukæmic blood they are not rare, but their significance in leukæmia is not known.[6 23] They are constantly and greatly increased in myelogenic leukæmia.[11]

ORIGIN, SIGNIFICANCE, AND FUNCTIONS. It has been suggested that mast-cells are wandering cells that have taken up disintegrating masses of chromatin;[5] that they have some relation with pigmentation, especially in the skin (Phillipson, cited by Bäumer);[3] that they perform an eliminative function in inflammation (Metschnikoff, cited by Bäumer);[3] also, that they may be formed by a metamorphosis of unstriped muscle-cells.[27] It is noticeable that the mast-cells seldom collect together in large masses, as plasma-cells often do. According to Unna,[39] urticaria pigmentosa forms a striking exception to the usual condition, as its lesions contain accumulations of mast-cells. This observation has been confirmed by others, including Bäumer,[3] who secured a somewhat similar condition by the repeated action of urtica urens on his own skin. Bäumer believed that the mast-cells originate from the connective tissue cells in the adventitia of the bloodvessels; these connective tissue cells showed numerous karyokinetic figures.

Concerning the significance and functions of mast-cells we are almost wholly in the dark. The staining properties of the granules are usually supposed to depend on peculiarities in their chemical composition. Ehrlich and Lazarus[11] regard them as a variety of granular leucocytes; according to Ehrlich's theory, the granules are products of the specific activities of these cells, resembling a secretion; each kind of leucocyte contains only one kind of granule; it is probable that the granules of the wandering cells are destined to be given off into the surrounding structures. From a recent article of Arnold,[1] it appears that he doubts whether all the cell granules are secretory in nature.

TECHNIQUE.

The fixation of the tissues may be accomplished in alcohol,[33] corrosive sublimate,[23] or Zenker's fluid.[9] Müller's fluid is apparently not applicable. The plasma cells are shown well after fixation in 4 per cent. formaldehyde, or in Müller-formol, but the staining of the granules of the mast-cells is modified as mentioned below.

Unna[37] explains the metachromism shown by the mast-cell granules and other bodies by supposing that solutions of the aniline dyes contain small quantities of other dyes as impurities. His alkaline methylene-blue, or "polychrome methylene-blue," is an extreme example, and he states that it contains methylene-violet and methylene-red in addition to methylene-blue.

Unna[33] has given several formulas for making polychrome methylene-blue, of which the following will be found satisfactory; it must stand several weeks to months before using:

Methylene-blue	1
Potassium carbonate	1
Distilled water	100

Sodium or ammonium carbonate may be used instead of potassium carbonate. To obtain the best results the specimens should be over-stained, the excess of color being removed with some decolorizing agent.

Stain in the methylene-blue solution, which may or may not be diluted, fifteen minutes or longer.

Rinse in distilled water.

Decolorize in water to which a few drops of "glycerin-ether" have been added, for a quarter of a minute, or for several minutes, as required, to show beginning differentiation of the structure.

Complete the decolorization with alcohol.

Clear in oil of bergamot or xylol.

One-half to one per cent. acetic acid solution appears to serve as well as glycerin-ether, and alcohol alone nearly as well.

By the above staining process the plasma-cells are stained a blue-violet, their nuclei and other nuclei blue, the granules of mast-cells red. Epithelial cells take the blue stain, sometimes intensely, especially the horny layers of the epidermis; giant-cells are frequently stained as well; also, the products of various degenerations, as amyloid and mucoid, which may show varying degrees of metachromism.[17] The development of a red color in the granules of the mast-cells is favored by extreme decolorization.

Nearly identical results, including the red color of the granules of the mast-cells, may be secured by employing watery solutions of thionin[16] or toluidin-blue, decolorizing with alcohol, or an acid followed by alcohol.[22] The plasma-cells often stain fairly well with ordinary methylene-blue solutions, and sometimes even with the other basic dyes. With basic dyes other than thionin, toluidin-blue, and polychrome methylene-blue, the granules of the mast-cells are well stained, but they are less easily distinguished, because the metachromism is much less pronounced. The mast-cell granules sometimes stain well with hæmatoxylin, but it is not clear under what conditions this occurs.

The writer has found that after fixation with formaldehyde or Müller-formol the mast-cell granules, after staining with polychrome methylene-blue, thionin or toluidin-blue, are colored *blue* or *violet* and *not red*, as occurs after alcohol or sublimate fixation, using two pieces of the same tissue, one fixed with alcohol, the other with formaldehyde, stained in the same solution; the granules of the mast-cells will be much redder in the specimen fixed by alcohol. This difference is most obvious after prolonged fixation and with frozen sections. It is more or less modified by paraffin or celloidin embedding, although the differences in color usually remain quite distinct after embedding. It appears equally well after decolorization with alcohol, acetic acid, and glycerin-ether, provided the decolorization is prolonged sufficiently. This work will be described in detail elsewhere.

In staining cover-glass preparations of blood, it is to be remembered that the granules of the mast-cells are not stained by the Ehrlich tricolor[11] mixture, although they may be stained by the simple basic dyes, such as methylene-blue.

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